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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/855,176	05/14/2001	Edward E. Knaus	RR-371 PCT/US CIP	8905

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EXAMINER
SCHNIZER, RICHARD A

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 01/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/855,176	Knaus et al
Examiner	**Art Unit**
Richard Schnizer	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 29, 2002*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-32* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *May 14, 2001* is/are a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☒ Certified copies of the priority documents have been received in Application No. *08/836,586*.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *3*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. The Examiner associated with this Application has changed. Please address further correspondence to Richard Schnizer, Art Unit 1635.

An amendment was received and entered as Paper No. 7 on 10/29/02. Applicant's election with traverse of Group I is acknowledged. After further consideration, the restriction requirement is withdrawn.

Claims 1-32 are pending and under consideration in this Office Action.

Priority

2. This Application is a continuation in part of 08/836,586, filed 10/20/95, abandoned, which claims priority to foreign application 9421223.0, filed 10/20/94. However, a review of the priority document finds no support for the limitation, recited in instant claim 6, wherein the "foreign gene is selected from eukaryotic or prokaryotic cells". Similarly, the priority document fails to support foreign gene selected from human cytomegalovirus, varicella zoster virus, or Epstein-Barr virus as recited in instant claim 8. Because claims 6 and 8 depend from claim 1, claim 1 is considered to embrace all of the limitations of claims 6 and 8, as do all of the dependents of claim 1 unless otherwise limited. It is found that all of claims 1-31 embrace the limitations of claims 6 and 8, therefore none of these claims can be awarded the priority date of 10/20/94. The priority date of claims 1-31 is considered to be 10/20/95.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

3. Claim 32 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-16, and 30-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *in vitro* methods of detecting gene transfer in a population of cells using (E)-5-(2-iodovinyl)-2'-deoxyuridine (IVDU) or IVDU-3' 1-methyl-1,4,dihydropyridyl-3-carbonyl (IVDU-CDS), does not reasonably provide enablement for *in vivo* methods of detecting gene transfer in a population of cells using IVDU or IVDU-CDS. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

5. In ex parte Forman, 230 USPQ 546 (bd. App. 1986) the board considered the issue of enablement in molecular biology and considered several factors. Consideration of these factors in the instant case follows.

Nature of the Invention

6. The inventions is a method of detecting gene transfer in a population of cells. In one embodiment the gene encodes a polypeptide capable of phosphorylating radiolabeled IVDU or IVDU-CDS, thereby sequestering IVDU or IVDU-CDS in cells containing the transferred gene. Non-phosphorylated IVDU and IVDU-CDS are not maintained within cells lacking an enzyme capable of phosphorylating these compounds. This allows non-invasive imaging of cells containing the delivered gene by, for example, scintigraphy detecting the location of radiolabelled IVDU or IVDU-CDS..

Breadth of the claims

7. The claims embrace both *in vivo* and *in vitro* methods.

State of the prior art, Predictability of the art, and Level of skill of those in the art

8. Prior to the time of the instant invention it was well known in the prior art that IVDU was unsuitable for in vivo administration and use in scintigrams because it was unstable and rapidly degraded to a substrate which could be sequestered nonspecifically in cells that did not contain the transferred gene. See e.g. Iwashina et al (Appl. Radiat. Isot. 41(7): 675-678 (1990), page 675,

column 2, lines 15-24, and Iwashina et al (Drug Design and Delivery (1988) 2(4): 309-321, sentence bridging pages 309 and 310). This is clear evidence that those of the highest skill in the art could not use IVDU for the purpose intended in the instant invention. Thus, while the art is predictable in this respect, the prediction is that the claimed invention would not function in the absence of further guidance not available in the art at the time of the invention. The art at the time of the invention also taught that it was unpredictable as to whether or not modification of IVDU with a 3' 1-methyl-1,4,dihydropyridyl-3-carbonyl moiety (IVDU-CDS) would result in stabilization and an improvement in specificity. Balzarini et al (Gene Therapy (7/1995) 2(5): 317-322) indicated that further study of CDS-modified IVDU was required to determine whether or not the modification had any effect on cellular delivery (see page 320, column 1, last sentence).

Guidance and working examples in the specification

9. The specification provides no working examples on the use of IVDU or IVDU-CDS in vivo for the detection of gene transfer, nor any guidance as to how to improve the stability and cellular specificity of either of these compounds without chemically altering the compounds themselves.

Amount of experimentation necessary

10. In view of the state of the art prior to the invention, the findings of those of skill in the art with respect to the in vivo lability of IVDU, the unpredictability of the in vivo lability of IVDU-CDS, and the lack of guidance and working examples in the specification, one of skill in the art

would have to perform undue experimentation in order to use IVDU or IVDU-CDS in an *in vivo* gene delivery detection method as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

12. Claims 1-32 are indefinite because it is unclear what constitutes "a substantial amount of the labelled compound". The speicification fails to define "substantial" in this context, and there is no art-recognized definition, so one of skill in the art cannot know the metes and bounds of the claims.

13. Claim 32 provides for the use of a labeled compound, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

14. Claims 1-13, 26, 27, and 30-32 are rejected under 35 U.S.C. 102(b) as being anticipated by Dougan (US Patent 5,248,771, issued 9/28/93).

15. Dougan teaches a diagnostic method for noninvasively detecting herpes virus infection. Selective uptake by infected cells of a radioactive (gamma ray emitting) antiviral drug serves as a substrate for virus-coded thymidine kinase. The "trapped" phosphorylated radioactive antiviral compounds can then be visualized using gamma ray scintigraphy or PET imaging. The substrate drug may be the compound according to instant claim 13 wherein R1 = OH, R2 = H, R3 = H, and R4 = H (i.e. IVAU or IvaraU). See column 2, lines 20-30, and column 2, lines 49-63. The radiolabel may be ^{123}I or ^{131}I (see column 8, lines 26-29.

16. Instant claim 2 requires isolation of a foreign gene from a cell or a virus, wherein the foreign gene is transferred into a population of cells and subsequently serves to produce a protein

that interacts with a labeled compound. Dougan teaches this aspect of the invention at column 15, lines 15-60. This section describes the infection of rabbits with herpes simplex virus comprising a thymidine kinase gene. Because herpes simplex virus must be produced in cells and isolated for use, the method of Dougan fairly suggests the isolation from cells of the Herpes virus and the Herpes virus thymidine kinase gene.

Thus Dougan anticipates the claims.

17. Claims 1-11, 13, 14, and 30-32 are rejected under 35 U.S.C. 102(b) as being unpatentable over Gill et al (Antimicrob. Agents and Chemother. (1984) 25(4): 476-478).

18. Gill teaches a method of quantitative analysis of the uptake of ^{131}I-labeled IVDU in cells that had been transfected with herpes virus thymidine kinase (see abstract, and page 476, column 2, last paragraph).

19. It is noted that the claims require "determining the extent and location of the protein throughout the population of cells". Gill meets the "extent" limitation because the labeled product was quantified. Gill meets the "location" limitation because the assay was performed on a population of cells, and the labeled product was determined to be located in the cells.

Thus Gill anticipates the claims.

20. Claims 1-13, 18, 19, and 30-32 are rejected under 35 U.S.C. 102(b) as being anticipated by Iwashina et al (Drug Design and Delivery (1988) 2(4): 309-321).

21. Iwashina teaches a method for noninvasive detection of herpes simplex encephalitis wherein radiolabeled IVFRU (instant claim 18) is administered to an animal, is acted on by herpes simplex thymidine kinase, the product is selectively trapped in cells, and detected by non-invasive means. The radiolabel may be ^{123}I. See abstract. With regard to instant claim 2, the method may be used in vitro on cells infected with TK+ herpes simplex virus. Such viruses, and their genes, are considered to be isolated from a cell prior to use, because viruses must be produced by infection and subsequent isolation from cells.

Thus Iwashina anticipates the claims.

22. Claims 1-15, 18, 19, 22, 23, and 30-32 are rejected under 35 U.S.C. 102(e) as being anticipated by Blasberg et al (US Patent 5,703,056, issued 12/30/97).

23. Blasberg teaches:

a method of detecting gene transfer to and expression in a target tissue of a host subject comprising:

(a) delivering to the target tissue of the host subject a transfer vector containing a marker gene not naturally present in the host subject wherein the marker gene is selected from the group consisting of wild-type, mutant or genetically engineered herpes simplex virus-thymidine kinase gene, and wherein the transfer vector is introduced to cells of the target tissue, and the marker gene is expressed in the cells of the target tissue, thereby generating a marker gene product which accumulates only in the cells containing the transfer vector;

(b) administering to the host subject a labeled marker substrate where cells expressing the marker gene product of step (a) metabolizes the labeled marker substrate to produce a labeled marker metabolite wherein the labeled marker substrate comprises a labeled 2'-fluoro-nucleoside analogue; and

(c) non-invasively imaging the target tissue or cells containing the labeled marker metabolite after clearance of residual marker substrate not metabolized by the marker gene product from said host subject thereby detecting gene transfer to and expression in the target tissue. See claim 1.

24. The marker substrate may be 5-[^{123}I]-, 5-[^{124} I]- or [^{131}I]-2'-fluoro-5-iodovinyl-1-beta-D-arabinofuranosyl-uracil (IVFAU), or 5-[^{123}I]-, 5-[^{124} I]- or 5-[^{131}I]-2'-fluoro-5-iodovinyl-1-beta-D-ribofuranosyl-uracil (IVFRU), or a 5-halo-2'-deoxyuridine (IVDU). See claim 13, and Table 4 at columns 21 and 22.

25. The marker gene may be herpes simplex virus thymidine kinase or it may be from a eukaryotic cell, i.e. yeast glucokinase or a cytochrome P-450 B1 gene (see column 6, lines 40-49).

26. The assay may also be performed *in vitro* for the purpose of comparing various radiolabelled substrates (see column 14, lines 23-40.

Thus Blasberg anticipates the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) a patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

27. Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gill et al (Antimicrob. Agents and Chemother. (1984) 25(4): 476-478) in view of Dougan (US Patent 5,248,771, issued 9/28/93).

28. Gill teaches an *in vitro* method of quantitative analysis of the uptake of ^{131}I-labeled IVDU in cells that had been transfected with herpes virus thymidine kinase (see abstract).

29. It is noted that the claims require "determining the extent and location of the protein throughout the population of cells". Gill meets the "extent" limitation because the labeled product was quantified. Gill meets the "location" limitation because the assay was performed on a population of cells, and the labeled product was determined to be located in the cells.

30. Gill does not teach ^{123}I labeled IVDU.

31. Dougan teaches a method of labeling synthetic substrates for detection of herpes virus thymidine kinase, and suggests the use of either ^{123}I or ^{131}I (see column 8, lines 26-29).

32. It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute an ^{123}I label for an ^{131}I in the method of Gill because these labels are obvious equivalents in that they would function similarly in the method, i.e. they would allow scanning and

quantification of cellular uptake of IVDU as suggested by Gill at page 476, column 1, last sentence. MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of *prima facie* obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945).

Thus the invention as a whole was prima facie obvious.

33. Claims 14-25, 28 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dougan (US Patent 5,248,771, issued 9/28/93) in view of Balzarini et al (Gene Therapy (7/1995) 2(5): 317-322).

34. Dougan teaches a diagnostic method for detecting herpes virus infection. Selective uptake by infected cells of a radioactive (gamma ray emitting) antiviral drug serves as a substrate for virus-coded thymidine kinase. The "trapped" phosphorylated radioactive antiviral compounds can then be visualized using gamma ray scintigraphy or PET imaging. The substrate drug may be the compound according to instant claim 13 wherein R1 = OH, R2 = H, R3 = H, and R4 = H (i.e. IVAU or IvaraU). See column 2, lines 20-30, and column 2, lines 49-63. The radiolabel may be ^{123}I or ^{131}I (see column 8, lines 26-29. The method may be performed in vitro. See column 13, lines 14-62.

35. Dougan does not teach the use of IVDU (instant claims 14 and 15), IVDU-CDS (instant claims 16 and 17), IVFRU (instant claims 18 and 19), IVFRU-CDS (instant claims 20 and 21), IVFAU (instant claims 22 and 23), or IVFAU-CDS (instant claims 24 and 25).

36. Balzarini teaches IVDU, IVDU-CDS, IVFRU, IVFRU-CDS, IVFAU, and IVFAU-CDS, and shows that these compounds are acted on by herpes virus thymidine kinase to produce cytostatic agents. See abstract.

37. It would have been obvious to one of ordinary skill in the art at the time of the invention to provide radiolabeled versions of the compounds of Balzarini, as taught by Dougan, and to substitute these for IVAU in the invention of Dougan. One would have been motivated to do so because IVDU-CDS, IVFRU, IVFRU-CDS, IVFAU, and IVFAU-CDS are obvious equivalents of IVAU in that they would reasonably be expected to function similarly in the method of Dougan, i.e. they would be phosphorylated by TK and entrapped in the target cells thereby allowing non-invasive detection of a radioactive label. MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of *prima facie* obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945).

Thus the invention as a whole was *prima facie* obvious.

Summary

Claims 1-16, and 30-32 are enabled for in vitro use of IVDU or IVDU-CDS, but not for the corresponding *in vivo* use.

Claims 1-14, 26, 27, and 30-32 are rejected under 35 USC 102(b).

Claims 1-15, 18, 19, 22, 23, and 30-32 are rejected under 35 USC 102(e).

Claims 14-25, 28, and 29 are rejected under 35 USC 103(a).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader, can be reached at 703-308-0447. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014. Additionally correspondence can be transmitted to the following RIGHTFAX numbers: 703-872-9306 for correspondence before final rejection, and 703-872-9307 for correspondence after final rejection.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

Richard Schnizer, Ph.D.

JEFFREY SIEW
PRIMARY EXAMINER
1/11/03